ORIGINAL ARTICLE INFECTIOUS DISEASES

Postprescription review improves in-hospital antibiotic use: A multicenter randomized controlled trial

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Abstract

Although review of antibiotic therapy is recommended to optimize antibiotic use, physicians do not always perform it. This trial aimed to evaluate the impact of a systematic postprescription review performed by antimicrobial stewardship program (ASP) infectious disease physicians (IDP) on the quality of in-hospital antibiotic use. A multicenter, prospective, randomized, parallel-group trial using the PROBE (Prospective Randomized Open-label Blinded Endpoint) methodology was conducted in eight surgical or medical wards of four hospitals. Two hundred forty-six patients receiving antibiotic therapy prescribed by ward physicians for less than 24 hours were randomized to receive either a systematic review by the ASP IDP at day 1 and days 3 to 4 (intervention group, n = 123) or no systematic review (usual care, n = 123). The primary outcome measure was appropriateness of antimicrobial therapy, a composite score of appropriateness of antibiotic use at days 3 to 4 and appropriate treatment duration, adjudicated by a blinded committee. Analyses were performed on an intention-to-treat basis. In the intervention group, appropriateness of antimicrobial therapy was more frequent (55/123, 44.7% vs. 35/123, 28.5%; odds ratio 2.03, 95% confidence interval 1.20–3.45). Antibiotic treatment duration was lower in the intervention group (median (interquartile range) 7 (3–9) days vs. 10 (7–12) days; p 0.003). ASP IDP counseling to change therapy was more frequent at days 3 to 4 than at day 1 (114/123; 92.7% vs. 24/123; 19.5%, p <0.001). Clinical outcome was similar between groups. This study suggests that a systematic postprescription antibiotic review performed at days 1 and 3 to 4 results in higher quality of antibiotic use and lower antibiotic duration. This trial was registered at ClinicalTrials.gov (NCT01136200).

Keywords: Antibiotic use, antimicrobial stewardship, hospital, infectious disease physician, review
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Introduction

Review of antibiotic therapy is of major importance to optimize the use of these drugs [1–3]. Antimicrobial stewardship programs (ASP) must thus include a strong incitation to prescribers to revaluate their prescriptions [2–6]. In France, early antibiotic revaluation was endorsed in 2011 by the Ministry of Health as a major component of ASP (http://www.sante.gouv.fr/). Some

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studies assessing the impact of review by the physicians themselves found it was modest at best [7–9]. This suggests that an assisted review is needed, which can be provided by ASP infectious disease physicians (IDP) dedicated to this work [9–16]. However, this approach has not been properly evaluated through a randomized multicenter trial in which criteria of appropriateness of antimicrobial use were adjudicated by independent investigators blinded to the randomization assignment.

We therefore undertook this trial to assess the impact of an ASP IDP-driven review and counselling as a tool to help physicians to optimize all antibiotic prescriptions. Our main objective was to assess whether this strategy would improve appropriateness of antibiotic use, as assessed by a blinded adjudication committee.

Methods

Study design and setting

The multicenter, prospective, randomized, parallel-group, open-label ANTIBIOREF trial was conducted between May 2010 and April 2011 at four university-affiliated hospitals in the Paris area. All had developed an ASP for several years, including a senior ASP IDP devoted to this work [16–19]. The trial was conducted in accordance with the Declaration of Helsinki and good clinical practices, and it complied with French regulatory requirements. It was approved by an ethics committee (Comité de Protection des Personnes Ile de France IX, advice no. 08 030). According to the French law, patients were informed before study inclusion of the conduct and objectives of the research by a written document; signed informed consent was waived, but patients had the right to opt out of participation.

This trial was registered at ClinicalTrials.gov (NCT01136200).

Wards

Two surgical or medical wards per hospital were selected as having a high level of antibiotic consumption with the perception of ASP IDPs that antibiotic use could be improved.

Patients

All patients hospitalized in participating wards receiving antibiotic therapy for $\leq$24 hours were assessed for eligibility by two independent physicians. Exclusion criteria were age <18 years, pregnancy, antibiotic prophylaxis for less than 24 hours and antibiotic prophylaxis for opportunistic infections.

Randomization and blinding

Patients were randomly assigned (1:1 ratio) to one of the two groups following a computer-generated randomization scheme, by blocks of variable and undisclosed size, stratified by hospital. The allocation sequence was concealed from the researcher enrolling and assessing participants by using a central fax randomization system.

Within the same 2-week period on a given ward, patients could be randomized to intervention or control arms. In order to control the risk of contamination of the usual care arm (global improvement of expertise in antibiotic use within a ward (i.e. in both trial arms) due to postprescription review and advice from the ASP IDP experts for the intervention arm patients), block periods of 15 days were preferred, separated by a sufficiently long period (6 months) to avoid the same residents being in the same ward at two different block periods (in France, residents rotate every 6 months).

Intervention

The prescription guidelines were reviewed and standardized in a common document. It was provided to participating ward physicians 1 month before starting the study.

For patients allocated to the intervention group, the ASP IDP visited the ward where the patient was housed at day 1 (D1) and days 3 or 4 (D3–D4) after the first prescription of antibiotic therapy during an in-hospital stay in the participating ward (weekdays only). He provided the prescribing physician with an oral recommendation to modify the antibiotic regimen when deemed appropriate, and he wrote his recommendations in the medical chart. Predefined criteria for antibiotic modification proposal were those used in a previous study [16].

For patients in the usual care group, the ASP IDP performed no systematic postprescription review. In this group, antibiotic review was left to the discretion of the ward physicians. Advice from the ASP IDP could be solicited by the physician if needed.

For both groups, the ward physician was the only prescriber; he was free to follow, or not follow, the ASP IDP advice. Compliance with ASP IDP advice included either complete or partial adherence to recommendations and was recorded in both groups.

Data collection

Data were collected by two independent physicians. Patients were followed until discharge from the hospital or transfer to another ward not participating to the trial. Sepsis and clinical improvement were defined according to previously published criteria [20–23].

Outcomes

Because investigator blinding to group assignment was not feasible, the main outcome criterion was adjudicated by an expert committee blinded to trial arm allocation according to PROBE (Prospective Randomized Open-label Blinded Endpoint) methodology [24]. At the end of follow-up, antibiotic

regimens administered at one site were reviewed by the ASP IDPs from the three other sites (which were therefore totally independent from the one that followed the patients) using a standardized report form. These adjudicators were not aware of the treating physician's notes and recommendations when they reviewed the chart documents. They adjudicated the appropriateness of the antibiotic regimen at the end of D1 and D3–D4 (at the time when IDP's recommendations were made and could be followed). Any disagreement between the three ASP IDP was further resolved by consensus to obtain complete agreement.

Because many aspects of antimicrobial prescribing were considered, we classified them into three major and six minor criteria [25]. Major criteria included the following: (a) treatment adequately pursued (or stopped if not indicated) at D3–D4, (b) optimal selection of drug at D3–D4 and (c) optimal duration of therapy (evaluated at the time of hospital discharge and defined as the duration recommended by the common guideline ±1 day). Minor criteria included (a) treatment adequately pursued (or stopped if not indicated) at D1, (b) drug used optimal at D1, and (c–f) modalities of administration and dosing optimal at D1and at D3–D4.

The primary outcome measure was the appropriateness of antimicrobial therapy, defined as the presence of all three major criteria. Secondary outcomes measures were appropriateness of antimicrobial therapy at D1 and D3–D4; duration of therapy; clinical improvement at day 3 and at discharge; in-hospital mortality; and length of hospital stay. Time required (visiting wards, contacting prescribers, issuing advice) and intervention cost were also evaluated as follows: time spent by the IDPs was estimated at hospital C. Antibiotic costs were estimated in all hospitals.

Statistical analysis

The trial was designed to determine whether the ASP IDP review was superior to usual care in terms of appropriateness of antibiotic use. Assuming a 50% rate of appropriate prescription in the control group, we hypothesized that the intervention might result in a 70% rate of appropriate prescriptions [16]. One hundred twenty-four patients per arm would provide 90% power at a two-sided level of 0.05 to detect such a difference.

Descriptive analyses were computed for the whole population by randomisation group and by hospital. Categorical outcomes were compared between groups by the chi-square or Fisher's test, as appropriate, and effect sizes were expressed as odds ratio (OR) and 95% confidence interval (CI). For continuous outcomes, groups were compared by Student *t* test or Wilcoxon test, as appropriate. Effect sizes were expressed as differences in means and their 95% CI.

All analyses were conducted on an intention-to-treat basis. Potential risk factors of the appropriateness of antimicrobial therapy were tested by univariate logistic regression analyses. Those associated at a level of 15% were retained to adjust for in a multivariate logistic regression.

We added sensitivity analyses in order to test the clustering effect of wards and hospitals using multilevel models analyses. We tested the influence of the between-ward (levels 1; wards nested in hospital) and between-hospital (level 2) variance on the effect on the principal end point.

Results

Study population

Among the 264 patients receiving antimicrobial therapy and screened for eligibility, 246 were randomized, 123 to the intervention group and 123 to the control group. All randomized patients were followed until hospital discharge.

The clinical characteristics were similar between the two groups (Table 1). Only 131 prescriptions (53.2%) were microbiologically documented at D3–D4.

In the intervention group, all prescriptions were reviewed at D1 and D3–D4 by the ASP IDP, who recommended a change in therapy for 24 (19.5%) at D1 and 114 (92.7%) at D3–D4 ($p < 0.001$). Most ASP IDP recommendations (21/22, 95.4% at D1; 106/114, 92.3% at D3–D4) were implemented by the wards' physicians. In contrast, the advice of the ASP IDPs were rarely solicited by physicians in the usual care group—for five patients (4.0%) at D1 and 19 patients (15.4%) at D3–D4.

Primary outcome

In all, 55 patients (44.7%) from the intervention group and 35 patients (28.5%) from the control group received appropriate antimicrobial therapy (Table 2). The OR of receiving appropriate therapy for the intervention group vs. controls was 2.03 (95% CI 1.20–3.45). In the univariate analysis, appropriateness differed according to the randomization group, clinical source of infection and Charlson score (Table 3). In the multivariate analysis, appropriateness was independently associated with the randomization group, community acquisition and clinical source and microbiologic documentation (Table 3). There was no centre effect (p 0.21). No significant clustering effect was observed for wards or for hospital.

Secondary outcomes

Appropriateness at D1 with regard to both antimicrobial treatment adequately pursued or stopped and optimal selection of drug was found for half of the prescriptions (Table 2) and did not differ significantly between the two groups (risk ratio 0.97;

TABLE 1. Baseline patient characteristics

Characteristic	Usual care (n = 123)	Intervention (n = 123)
Sex		
Male	69 (56.1)	72 (58.5)
Female	54 (43.9)	51 (41.5)
Age (years)	70 (54.5–79)	65 (55–78)
Hospital		
A	17 (13.8)	14 (11.4)
B	38 (30.9)	35 (28.4)
C	50 (40.7)	53 (43.1)
D	18 (14.6)	21 (17.1)
Ward		
Surgical	20 (16.3)	17 (13.8)
Medical	103 (83.7)	106 (86.2)
McCabe and Jackson classification		
Nonfatal underlying disease	56 (45.5)	61 (49.6)
Ultimately fatal underlying disease	54 (43.9)	57 (46.3)
Rapidly fatal underlying disease	13 (10.6)	5 (4.1)
Charlson score	2 (0–3)	2 (0.5–3)
Immunosuppression*	20 (16.3)	17 (13.8)
Acquisition of infection		
Community acquired	64 (52.0)	57 (46.3)
Healthcare associated	12 (9.8)	19 (15.4)
Hospital acquired	47 (38.2)	47 (38.2)
Clinical source of infection		
Urinary tract	39 (31.7)	29 (23.6)
Lower respiratory tract	19 (15.4)	14 (11.4)
Digestive tract	18 (14.6)	20 (16.3)
Skin and soft tissues	12 (9.7)	7 (5.7)
Other site	12 (9.7)	18 (14.6)
Colonization†	4 (3.2)	7 (5.7)
None	19 (15.4)	28 (22.7)
Severe sepsis or septic shock	4 (3.3)	5 (4.1)
Bacteremia	5 (4.1)	10 (8.1)
Microbiologic documentation at day 3–4	61 (49.6)	70 (56.9)
Total number of pathogens	72 14 (19.4)	85 19 (22.3)
Streptococcus spp.		
Staphylococcus spp.	7 (9.7)	10 (11.7)
Enterobacteriaceae	39 (54.1)	37 (43.5)
Others	12 (16.6)	19 (22.3)
Polymicrobial infection	12 (9.7)	18 (14.6)
WBC count (/mm^3)	10 800 (8000–13 880)	10 650 (7300–15 780)
C-reactive protein (mg/L)	99 (36–201)	86 (17–185)

WBC, white blood cell count.
Data are shown as n (%) or median (interquartile range).
*Defined by the presence of neutropenia (absolute neutrophil count <500/mm^3), or human immunodeficiency virus infection, or corticosteroid therapy (prednisone > 0.3 mg/kg per day for at least 15 days in the last 3 months) or other immunosuppressive therapy.
†Antibiotic treatment for asymptomatic bacteriuria before surgical procedure of the urinary tract.

95% CI 0.59–1.60). In contrast, ASP IDP review led to a significant increase of the appropriateness at D3–D4 with respect to these two criteria either combined (risk ratio: 2.19; 95% CI 1.29–3.71) or separately evaluated (antibiotic indicated or stopped, risk ratio 2.09; 95% CI 1.03–4.22; and optimal drug, risk ratio 2.22; 95% CI 1.20–4.11). The ASP IDP counselling also led to a significantly higher appropriate duration of therapy (OR 1.75; 95% CI 1.05–2.89) and a reduction of antibiotic exposure in patients. The difference was 3.1 days (95% CI 0.97–5.25) (Student t test p 0.003).

Clinical end points

Clinical end points did not differ significantly between the intervention and control groups (Table 4). Therefore, no apparent detrimental effect was found to be associated with the lower antibiotic exposure in patients of the intervention group. Only one patient (intervention group) died; his death was due to an underlying event (refractory cardiogenic shock) considered to be unrelated to the intervention.

Time required and intervention cost

Median intervention time of ASP from the data from hospital C was 40 (interquartile range (IQR) 30–50) minutes for surgical wards and 40 (IQR 30–40) for medical wards, giving a median cost of ASP IDP per patient of €56.6 and €67.2 in the surgical and medical wards, respectively. Median antibiotic total cost per patient was of €19.0 (IQR €8.0–37.8). Median time of hospitalization was 4.0 days (IQR 2.0–6.0 days). The cost of a public hospital stay per day in medical or surgical wards is €781.52.

Taking into account the antibiotic total cost, length of hospitalization and intervention cost of ASP IDP, we estimated the median total cost per patient to be €1626 (IQR €90.7–3967) in the intervention arm and €1646 (IQR €114.6–3986) in the control arm. The difference was not significantly different between arms (p 0.33; Wilcoxon test).

Agreement between experts of adjudication committee

Proportion of agreement between the three assessors was relatively high for antimicrobial treatment adequately pursued or stopped (D1, n = 169, 68.7%; D3–D4, n = 188, 76.4%), optimal drug at D3–D4 (n = 163, 66.2%), optimal dosing (D1, n = 174, 70.7%; D3–D4, n = 198, 80.5%) and modalities of administration (D1, n = 207, 84.1%; D3–D4 (n = 230, 93.5%). In contrast, rates of agreement were lower for optimal drug at D1 (n = 127, 51.6%) and optimal duration of therapy (n = 122, 49.6%).

Discussion

This multicenter, randomized trial including 246 patients receiving antimicrobial therapy at admission or during their stay in surgical and medical wards demonstrated that an ASP IDP review results in improved quality of antibiotic use. Moreover, this strategy markedly reduced the antibiotic exposure of patients without apparent adverse effects.

Review of antibiotic therapy aimed at increasing its appropriateness should cover all aspects of prescribing [5,18]. It was implemented in some hospitals and showed efficacy in improving antimicrobial use [10–12,15,26], high compliance of prescribers and a favourable impact on resistant bacterial pathogens [10,12,13,27]. However, there were some limitations of these studies because of their design. In this study, we chose to include patients regardless of the antibiotic used, and the multicenter and randomized design allowed us to

TABLE 2. Main outcome measures

Variable	Usual care (n = 123)	Intervention (n = 123)	p
Main outcome criteria*	35 (28.5)	55 (44.7)	0.008
Secondary outcome criteria			
Day 1			
Antibiotic indicated or adequately stopped	96 (78.0)	89 (72.4)	0.30
Optimal drug	62/96 (64.6)	61/89 (69.5)	0.57
Two criteria above	62 (50.4)	61 (49.6)	0.9
Optimal administration	87/96 (90.6)	81/89 (91.0)	0.93
Optimal dosing	78/96 (81.2)	68/89 (76.4)	0.42
Day 3–4			
Antibiotic indicated or adequately stopped	97 (78.9)	109 (88.6)	0.04
Optimal drug	61/99 (61.6)	82/105 (78.1)	0.01
Two criteria above	60/120 (50.0)	81/118 (68.6)	0.003
Optimal administration	79/87 (90.8)	77/81 (95.1)	0.28
Optimal dosing	77/87 (88.5)	74/81 (91.4)	0.54
Optimal duration	55 (44.7)	72 (58.5)	0.03
Duration (days)	10 (7–16)	7 (3–14)	0.003

Data are shown as n (%) or median (interquartile range).
*Primary outcome measure was appropriateness of antimicrobial therapy defined by (a) antibiotic indicated at days 3 and 4 (D3–D4) (or stopped if judged unnecessary), (b) optimal drug at D3–D4 and (c) adequate duration according to joint guidelines.

demonstrate its effectiveness and feasibility with good internal and external validity. Importantly, it led to lower antibiotic exposure in patients without detrimental clinical effects, further confirming the lack of unintended clinical consequences of these interventions [5,6].

Because ASP IDP resources are scarce in hospitals, identifying determinants of efficacy could help focus intervention on specific types of patients. Apart from ASP IDP review, three other variables (acquisition of infection, clinical source and microbiologic documentation) were associated with appropriateness of therapy [17,28]. Moreover, we were able to evaluate the potential impact of ASP IDP counselling at two different times of the prescription. To increase their efficiency, our results suggest targeting ASP IDP interventions at D3–D4 after initiation of therapy.

The rates of appropriateness in both groups were lower than expected. This may be explained by our main outcome criterion: it included the appropriateness of duration of therapy, which has rarely been taken into account in previous studies [1,10,11,15]. In fact, appropriate duration was less frequently achieved than other components of the composite criterion. Excluding duration from the definition increases the appropriateness in both groups (control group 28.4% to 50.0%; intervention group 44.7% to 68.8%), and the difference remained in favour of the intervention. Further, optimal duration was defined as the duration recommended by our common guideline ±1 day. It can be argued that this was a too strict a quality assessment of the antibiotic prescription [1,25].

Contrary to all previous studies, prescriptions were evaluated by independent investigators blinded to the randomization assignment [10,26]. Although there was a good agreement with regard to many components of the prescription, the investigators met more difficulties in finding an agreement for optimal drug and duration. Our data suggest that in further studies, appropriateness should be reviewed by a blinded adjudication committee.

Several limitations should be mentioned. First, our study had an open design and involved only surgical or medical wards. Therefore, the results ought not be extended to intensive care units or haematology wards [29]. It should also be noted that the study was conducted in hospitals with a long experience of ASP. These may explain the high compliance of physicians, which was a key component of the success of the intervention [16]. On the other hand, we did not randomize treating physicians but rather the patients; thus, potential contamination between the intervention and control groups may have diminished the measure of the effect of the intervention.

To conclude, ASP IDP systematic review was a useful method to improve the appropriateness of therapy in surgical and medical wards. It also resulted in shorter antibiotic exposure without negative clinical effects. Postprescription antibiotic review is a major component of ASP and may be implemented in many hospitals.

Transparency declaration

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TABLE 3. Analysis of factors associated with appropriateness of antimicrobial therapy

	Univariate analysis			Multivariate analysis		
Characteristic	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Sex			0.24			
Female (Ref.)	1					
Male	1.4	0.8–2.3				
Age, per 10 years	1	0.9–1.1	0.89			
Hospital			0.29			
A (Ref.)	1					
B	1.4	0.5–3.6				
C	2.1	0.9–5.2				
D	1.6	0.6–4.5				
Ward			0.08			0.21
Surgical (Ref.)	1			1		
Medical	1.8	0.9–3.6		1.7	0.7–4.1	
McCabe classification			0.56			
Nonfatal underlying disease (Ref.)	1					
Ultimately or rapidly fatal	0.9	0.5–1.4				
Charlson score			0.026			0.10
<4 (Ref.)	1			1		
≥4	0.5	0.2–0.9		0.5	0.2–1.1	
Immunosuppression			0.18			
No (Ref.)	1					
Yes	0.6	0.3–1.3				
Acquisition of infection			0.13			0.01
Community acquired (Ref.)	1			1		
Health care or hospital acquired	0.7	0.4–1.1		0.4	0.4–0.8	
Clinical source of infection			0.01			0.02
Urinary tract (Ref.)	1			1		
Lower respiratory tract	0.4	0.2–1.2		0.6	0.2–1.8	
Digestive tract	1.8	0.8–4.0		1.2	0.4–3.5	
Skin and soft tissues	0.4	0.1–1.4		0.4	0.1–1.5	
Other site	1.0	0.4–2.4		1.1	0.4–2.9	
Prophylaxis	3.4	0.9–12.9		4.7	1.1–19.8	
None	1.9	0.9–4.0		2.3	1.0–5.5	
Sepsis			0.46			
Yes (Ref.)	1					
No	0.8	0.5–1.4				
Microbiologic documentation			0.06			0.03
No (Ref.)	1			1		
Yes	1.7	1.0–2.8		2.1	1.1–4.1	
Randomization group			0.01			0.04
Control (Ref.)	1			1		
Intervention	2.0	1.2–3.5		1.8	1.0–3.2	

OR, odds ratio; CI, confidence interval.

TABLE 4. Clinical outcome of included patients

Outcome	**Control (n = 123)**	**Intervention (n = 123)**	**p**
Clinical improvement at day 3	95 (77.2)	99 (80.5)	0.53
Clinical improvement at discharge for patients discharged after day 3*	51/63 (80.9)	60/68 (88.2)	0.25
In-hospital mortality	0 (0)	1 (0.8)	1
Length of stay (days)	4 (2–6)	4 (2–6)	0.55

Data are shown as n (%) or median (interquartile range).
*Data were missing for 60 subjects in the control group and 55 in the intervention group.

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